Human ESC-Derived Neural Crest Model Reveals a Key Role for SOX2 in Sensory Neurogenesis.

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Public Summary:
SOX2 is a transcription factor with capital importance in central nervous system development and neural precursor cell (NPC) biology, which is witnessed by the severe phenotypes observed in humans with SOX2 mutations. SOX2 haploinsufficiency syndrome manifests in fact with absence of eyes, abnormal hippocampus development and intellectual deficits among others. However, little was known about the role of this gene in peripheral nervous system (PNS) development. NPCs of the peripheral nervous system arise from a developmental population of cells termed neural crest (NC). In this work we explored the role of SOX2 in NC cells and the genesis of peripheral sensory neurons. By using a combination of transgenic mice and human embryonic derived-NC cells to model the peripheral nervous system development we showed that, in post-migratory NC cells, SOX2 is re-expressed in sensory neuron precursor of the dorsal root ganglia and it acts in this type of NPCs as a pluripotency factor by conferring such cells the ability to become neurons. In the absence of SOX2, NPCs fail to respond to neurogenic cues, fail to up-regulate pro-neural genes required for neuronal differentiation and, ultimately, die. This is first report showing a critical role of SOX2 in peripheral nervous system development and might explain why SOX2 mutations in human have some pathological features in common with the neural crest-related pathology CHARGE, such as sensorineural deafness.

Scientific Abstract:
The transcription factor SOX2 is widely known to play a critical role in the central nervous system; however, its role in peripheral neurogenesis remains poorly understood. We recently developed an hESC-based model in which migratory cells undergo epithelial to mesenchymal transition (EMT) to acquire properties of neural crest (NC) cells. In this model, we found that migratory NC progenitors downregulate SOX2, but then start re-expressing SOX2 as they differentiate to form neurogenic dorsal root ganglion (DRG)-like clusters. SOX2 downregulation was sufficient to induce EMT and resulted in massive apoptosis when neuronal differentiation was induced. In vivo, downregulation of SOX2 in chick and mouse NC cells significantly reduced the numbers of neurons within DRG. We found that SOX2 binds directly to NGN1 and MASH1 promoters and is required for their expression. Our data suggest that SOX2 plays a key role for NGN1-dependent acquisition of neuronal fates in sensory ganglia.